

## Radiology Corner

### Tuberous Sclerosis with Epilepsy

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*Note: This is the full text version of the **Radiology Corner** question published in the January 2009 issue, with the abbreviated answer in the February 2009 issue.*

This case report is designed to familiarize military physicians with findings common in tuberous sclerosis patients with epilepsy. Tuberous sclerosis is an inherited multi-system disorder that typically causes benign hamartomas to develop in vital organs. When this occurs in the brain, the hamartomas may lead to neurological disorders such as epilepsy. TS has an incidence of approximately 1 in 6000 live births. Although diagnosis of tuberous sclerosis is often made clinically, radiographic images such as those provided by magnetic resonance imaging are paramount in determining the most effective management and treatment of tuberous sclerosis.

#### Introduction

Tuberous sclerosis (TS), also known as Bourneville's disease, is characterized by benign tumor growths in vital organs such as the brain, heart, kidney, lungs, skin, and eyes. TS has an incidence of approximately 1 in 6000 live births (1). Although individuals with this condition are ineligible for military service, it is a genetic disorder that may go undiagnosed into adulthood. In addition, it may occur in dependents of military service members where neither parent has the clinical disorder. The large amount of variability within clinical presentation of TS allows it to be easily confused with other medical conditions. In addition to neurological conditions such as epilepsy, roughly 50% of individuals with TS have learning difficulties that include autism, attention-deficit hyperactivity disorder (ADHD), behavioral issues, developmental disability, and obsessive compulsive disorder (2).

#### History

This patient is a 13 year old girl with a history of intractable complex partial seizures that began at 5 months of age. She also has mental deficiency, two small benign tumors on her heart, and numerous hypomelanotic macules (one shaped like an ash leaf inferior to her umbilicus) in addition to her

multiple hospitalizations for seizures. She uses a vagal nerve stimulator (VNS) set at maximum level, and she is maintained on a modified ketogenic diet to help control seizure activity. Her medications include levetiracetam, primidone, lamotrigine, clonazepam, depot medroxyprogesterone acetate, and diazepam.

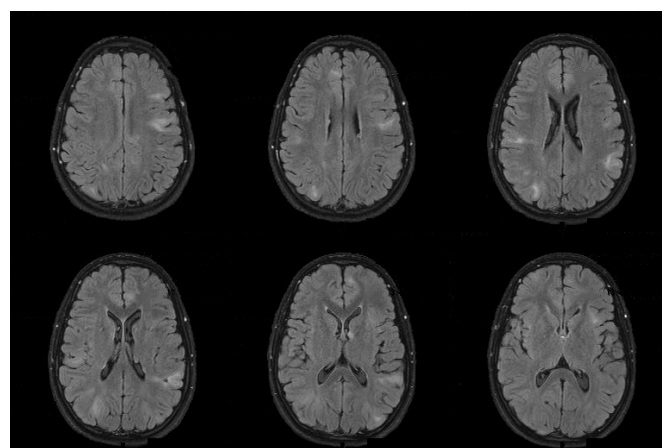


Fig. 1 MRI T1 axial showing high signal cortical lesions and mixed signal intensities.

#### Summary of Image Findings

Axial and coronal head T1 weighted magnetic resonance imaging (MRI) demonstrate several cortical lesions with high signal and mixed signal intensities (Fig. 1, 2). Axial and coronal head T2 weighted MRI show multiple calcified subependymal nodules along the lateral ventricles (Fig. 3). Further studies compared T1 weighted MRI with fluorodeoxyglucose <sup>18</sup>F (<sup>18</sup>F-FDG) positron emission tomography (PET) showing abnormal cerebral glucose metabolism that is evident as multiple areas of decreased metabolism in the regions of the cortical tubers (Fig. 4).

The study also compared the T1 weighted MRI with an alpha-<sup>11</sup>C-methyl-L-tryptophan (AMT) PET scan in the region adjacent to the tuber labeled as 7 in the left frontal cortex (Fig. 4). This is shown in planes 13, 14, and 15 with increased AMT uptake. This signifies an increased possibility that tuber 7 is an epileptogenic tuber (benign tumor that is the cause of recurrent seizures).

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Report Documentation Page				Form Approved OMB No. 0704-0188	
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1. REPORT DATE <b>FEB 2009</b>		2. REPORT TYPE		3. DATES COVERED <b>00-00-2009 to 00-00-2009</b>	
4. TITLE AND SUBTITLE <b>Tuberous Sclerosis with Epilepsy</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Uniformed Services University of the Health Sciences, Department of Radiology and Radiological Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release; distribution unlimited</b>					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>Same as Report (SAR)</b>	18. NUMBER OF PAGES <b>4</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

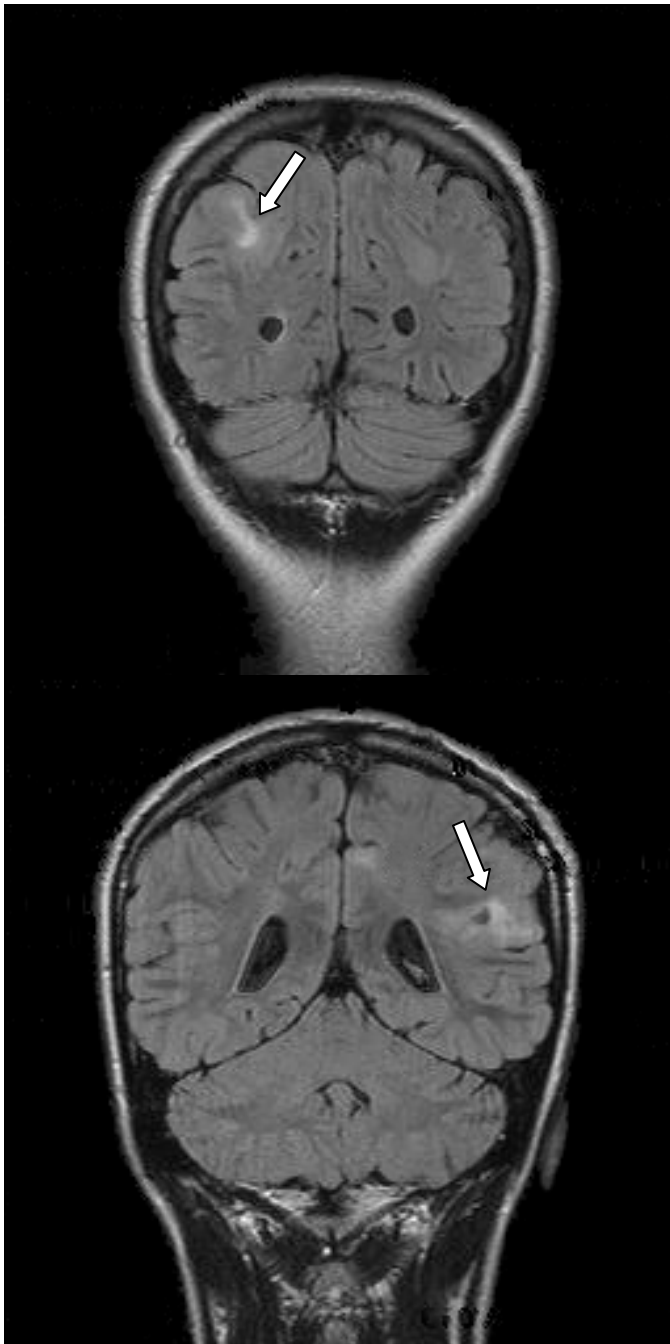


Fig. 2: MRI T1 coronals showing high signal cortical lesions (arrows) and mixed signal intensities.

### Patient Discussion

Differential considerations for abnormal cortical lesions with high signal and mixed signal intensities include multiple sclerosis, encephalitis, neuronal migration disorders, multiple gliomas, and cortical contusions. However, the differential diagnosis for multiple subependymal calcifications/nodules is principally limited to TS and some congenital infections such as cytomegalovirus, rubella, and toxoplasmosis. Multiple sclerosis is an autoimmune disorder in which the body attacks neuronal tissue leading to demyelination of the nerve cells that may appear as asymmetrical cortical lesions on

MRI. Encephalitis is an acute inflammation typically caused by viral or bacterial agents that may appear as cortical lesions on MRI. Neuronal migration disorder is a general term for a group of birth defects that occur due to abnormal neuron migration during fetal development that may lead to abnormal MRI findings such as cortical lesions. Grey matter heterotopias are lesions of grey matter located in incorrect locations within the brain including subependymal regions.

The diagnosis of TS is based upon specific clinical features, which are separated into two categories of major and minor features. Diagnostic certainty for TS is determined by the number of features and the category of these diagnostic features. A definite diagnosis is classified as two major features or one major and two minor features. Probable diagnosis is classified as a major feature in addition to one minor feature. The final level of diagnostic certainty is called suspect, which requires either one major feature or two or more minor features (3).

Accepted major features of TS include findings such as facial angiofibromas (also known as adenoma sebaceum), shagreen patches (connective tissue nevus), three or more hypomelanotic macules, nontraumatic ungula or periungual fibromas, lymphangioleiomyomatosis (also known as lymphangiomyomatosis), renal angiomyolipomas, cardiac rhabdomyomas, multiple retinal nodular hamartomas, cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. The minor features of TS include, but are not limited to, confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules), gingival fibromas, multiple randomly-distributed pits in dental enamel, hamartomatous rectal polyps, multiple renal cysts, non-renal hamartomas, bone cysts, retinal achromic patches, and cerebral white matter radial migration lines. At 18 months of age and after several seizures, this patient finally had a diagnosis. A further work-up showed that the patient also had 2 small cardiac rhabdomyomas, 26 cortical tubers, and subependymal nodules. The patient met the TS criteria at this point with three major features. She was later diagnosed with epilepsy due to the recurrent similar seizures. This patient required radiographic and nuclear imaging studies to determine the best course of action (3).

Management of children who have TS with epilepsy depends upon individual circumstances and can include antiepileptic drugs such as phenytoin, carbamazepine, valproic acid, ethosuximide, phenytoin, phenobarbital, zonisamide and/or nonpharmacologic therapies. Progesterone therapy also seems to have some anticonvulsant effects and may be used as an adjunct in treatment particularly if symptoms occur around menses (4). "Timely surgical resection of the epileptogenic tubers should be considered" (5) in children with TS and drug-resistant epilepsy. However, surgical intervention may not always be the best solution. This is true in this patient's case where widespread distribution of tubers in key functional areas and conflicting data between the AMT PET and

magnetoencephalography (MEG) confuse the epileptogenic tuber(s).

In addition to surgical intervention and the medications previously listed, alternative possibilities that may be used separately or together in seizures refractory to medical treatment include ketogenic diet or VNS. The anticonvulsant effects of the ketogenic diet are a result of the persistent state of ketosis (6). VNS involves intermittent stimulation of the vagus nerve which has proven to be effective in reducing seizure frequency (7). In this patient's situation improved seizure control was achieved with a combination of a modified ketogenic diet, VNS, and depot medroxyprogesterone acetate. An important consideration before deciding to implant VNS is the negative effects of image quality, even when the device is turned off and capability from susceptibility effects of future MRI and MEG studies. The VNS can be surgically removed except for the leads attached to the vagus nerve, which would still cause interference with the image quality. This patient was not able to have a quality MEG due to the interference from the VNS.

### Discussion

TS is an autosomal dominant genetic disorder that is caused by either a gene mutation known as tuberous sclerosis complex 1 (TSC1) or TSC2. TSC1 gene mutations maps to chromosome 9q34 and encodes the widely expressed tumor suppressor protein hamartin (8). TSC2 gene mutations maps to chromosome 16p13.3 and encodes the protein tuberin, which is known to form a complex with the protein hamartin and participates in normal brain development (9). The hamartin and tuberin complex works as a GTPase that suppresses mTOR signaling in the genetic control of cell growth and division (10). The data is conflicting in regards to whether the frequency of mental deficiency differs between the TSC1 and TSC2 genotypes; however, there are studies that propose that TSC2 genotype has a higher occurrence of more severe phenotypical neurologic problems than the TSC1 mutation (11).

Neurological manifestations of TS include cortical tubers, white matter heterotopia, subependymal nodules, and subependymal giant cell astrocytomas. Cortical tubers are enlarged atypical neuronal and glial components with astrocytosis. Subependymal nodules extend out into the ventricles and are part of a subtype of hamartoma known as glioneuronal hamartomas (12). These findings of TS manifest themselves symptomatically as seizures, epilepsy, and learning disabilities including autism, ADHD, behavioral issues, mental deficiency, and obsessive compulsive disorder. Historically, the classic clinical diagnosis of TS was based on Vogt's triad, which consists of seizures, mental deficiency, and facial angiofibromas, however, it occurs in fewer than 50 percent of patients (13). In the evaluation of epilepsy, MEG can be used in conjunction with MRI to localize the source of the seizures as well as assessing the normal electrical activity of adjacent areas of the brain.

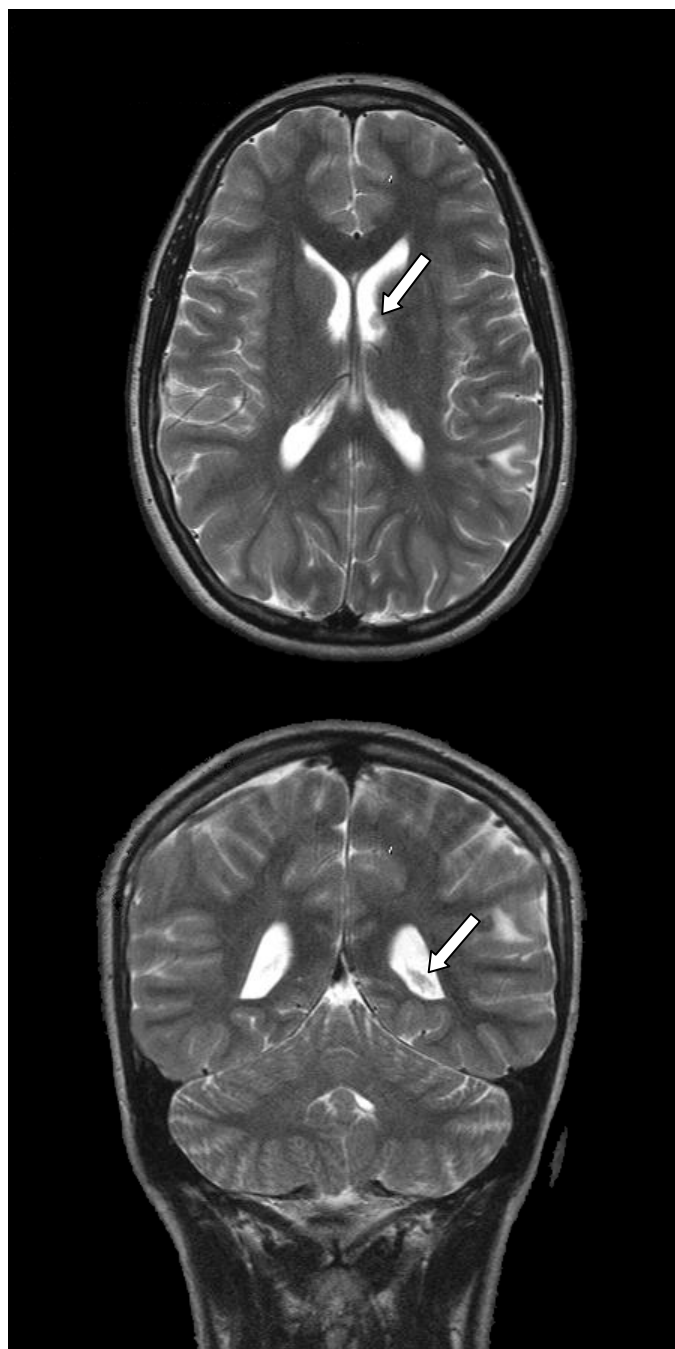
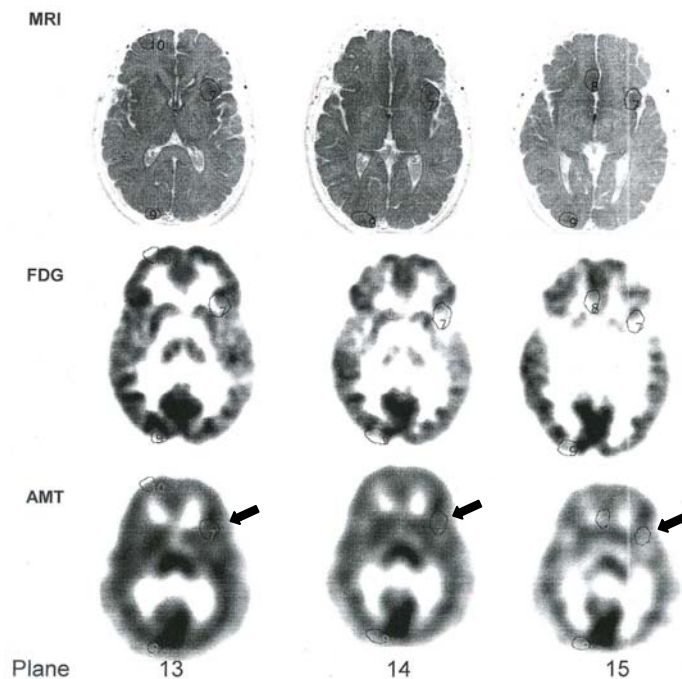


Fig. 3: MRI T2 axial (top) and coronal (bottom) showing subependymal calcifications/nodules in lateral ventricles (arrows).

The use of radiographic imaging such as MRI and nuclear medicine studies such as AMT PET scans play a crucial role in detection and management of TS. T1, T2, FLAIR, and contrast-enhanced MR images are used to detect cortical tubers, subependymal nodules, subependymal giant cell astrocytoma, radial migration lines, and microcephaly, all findings often seen in and diagnostic of TS (5). 90% of TS patients have seizures and 25 to 30% of them have intractable epilepsy (14). Typically, the TS patient's first seizure occurs during infancy and the natural progression of epilepsy is depicted by increasing frequency and severity of seizures, decreased response to antiepileptic drugs, and a reduced

quality of life due to the seizures and adverse medication effects (5). The patients, who are often children, may have multiple tubers within the cerebral cortex, and the epileptogenic tuber is often difficult to identify with conventional MRI or video electroencephalography alone.



**Fig. 4** FDG PET shows abnormal cerebral glucose metabolism is evident where there are multiple areas of hypometabolism in the regions of the cortical tubers. AMT PET scan: The region adjacent to tuber #7 in the left frontal cortex (arrow) shown in planes 13, 14, and 15 has increased AMT uptake.

Diffusion tensor MRI and PET/MRI fusion imaging with  $^{18}\text{F}$ -FDG PET or AMT PET have been used in the analysis of epilepsy in TS patients. The diffusion tensor MRI has two critical factors: the apparent diffusion coefficient (a measure of the overall magnitude of water diffusion) and fractional anisotropy value (a measure of the directionality of diffusion motion) (5). In TS, the tubers will have a high apparent diffusion coefficient, perilesional white matter indicating gliosis and/or hypomyelination, and a low fractional anisotropy when using diffusion tensor imaging (15). The imaging information obtained from the study is used to interpret the propagation arrangement of epileptic seizures and aid in determination of the cognitive impairment in TS patients with chronic epilepsy (5). The integration of  $^{18}\text{F}$ -FDG PET and AMT PET with MR images has shown an increase in sensitivity and specificity in identifying epileptogenic tubers by means of a noninvasive study (5).

In conclusion, MRI in conjunction with  $^{18}\text{F}$ -FDG PET and AMT PET are useful studies to help determine the most effective treatment for TS patients with epilepsy. This case also illustrates the potential anticonvulsive effects of a properly titrated ketogenic diet, antiepileptic medications, and VNS. Effective detection and treatment of epilepsy in TS patients will help increase positive outcomes, boosting the morale of those service members who themselves have TS or whose dependents have TS.

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